

PURINE-BASED NNRTIS SHOWING HIGH EFFICACY AND LOW CYTOTOXICITY IN CELL CULTURE AGAINST MULTIPLE NNRTI-RESISTANCE MUTATIONS

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Diarylpyrimidine (DAPY) compounds continue to show tremendous potential as nonnucleoside reverse transcriptase inhibitors (NNRTIs). Etravirine was recently approved by the FDA. Several other DAPY compounds are in advanced clinical trials and there is evidence that they are effective against not only wild-type HIV-1, but also most known NNRTI-resistant HIV-1 mutants. In addition, dapivirine is being tested as a chemoprophylactic agent. Chemoprophylaxis is a promising approach to limiting the spread of HIV-1 in the absence of a preventive vaccine. However, giving a drug to uninfected people over a prolonged period of time requires that the drug be not only highly effective, but minimally toxic as well. We have developed derivatives of TMC278 (rilpivirine), one of the DAPY compounds, with purine in place of the pyrimidine. These compounds show comparable efficacy to rilpivirine in luciferase-based infectivity assays in cell culture and cells remain viable at similar to moderately higher concentrations than with rilpivirine. Interestingly, retaining a paramethoxybenzyl (PMB) group at the N9 position of the purine, added during synthesis as a protecting group, increases the CC_{50} value dramatically with a relatively modest effect on IC_{50} values. Four compounds have been selected for further testing. Analyses of each compound's effects on viral DNA synthesis in real time are nearing completion at the time of this writing. Computer modeling of each compound's interactions with RT have been performed and will soon be compared to crystallographic data. This structural data should provide valuable insight regarding the role of the PMB group and whether other functional groups can be used to optimize interactions. The combination of highly effective inhibition against multiple NNRTI-resistant strains of HIV-1 with a more favorable cytotoxicity profile make these compounds interesting candidates not only as therapeutic drugs, but also as chemoprophylactic agents.